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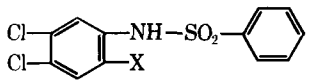
Preparation and Antitumor Activity of Some Schiff Bases of 2′-Amino-4′,5′-dichlorobenzenesulfonanilide and 2′-Amino-*p*-toluenesulfonanilide

JOHN H. BILLMAN and ROBERT L. SCHMIDGALL

Abstract □ Series of variously substituted salicylaldehyde Schiff bases and 2-substituted-*p*-[*N*,*N*-bis(2-chloroethyl)amino]benzaldehyde Schiff bases of 2′-amino-4′,5′-dichlorobenzenesulfonanilide and 2′-amino-*p*-toluenesulfonanilide have been prepared and screened for antitumor activity. None of the compounds showed appreciable activity against L-1210 leukemia.

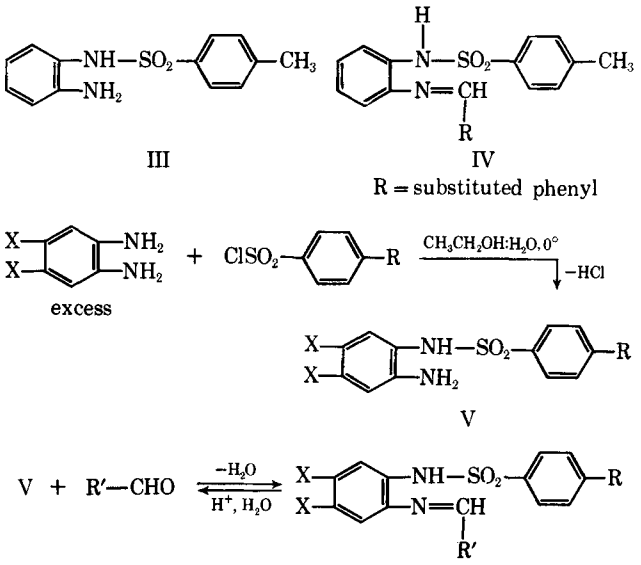
Keyphrases □ 2′-Amino-4′,5′-dichlorobenzenesulfonanilide, Schiff bases—synthesis, antitumor activity evaluation □ 2′-Amino-*p*-toluenesulfonanilide, Schiff bases—synthesis, antitumor activity evaluation □ Antitumor activity evaluation—2′-amino-4′,5′-dichlorobenzenesulfonanilide, 2′-amino-*p*-toluenesulfonanilide □ IR spectrophotometry—structure, analysis

Woolley *et al.* (1–3) have shown that 4′,5′-dichloro-2′-nitrobenzenesulfonanilide (I*a*) is effective in permanently curing some spontaneous mammary cancers of mice. Evidently the not very toxic I*a* functions as an antimetabolite of 1,2-dimethyl-4,5-diaminobenzene and inhibits the biosynthesis of vitamin B_{12}, which is synthesized by the spontaneous cancers but not by the hosts (4). 2′-Amino-4′,5′-dichlorobenzenesulfonanilide (I*b*) was also apparently active but much less potent than I*a*.



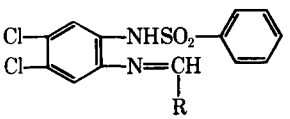
I*a*, X = —NO_2
I*b*, X = —NH_2

In view of the antitumor activity or at least accessibility to the tumor site of I*a* and I*b* plus the convenient handle of the primary amino group of I*b* for further structural modifications, it was decided to prepare some derivatives of Type II. Twelve of these derivatives (Table I) were conveniently synthesized (Scheme I) by condensing the desired aldehyde with I*b*, which was prepared from the corresponding *o*-phenylenediamine and arylsulfonyl chloride. The aldehydes employed were those substituted salicylaldehydes and 2-substituted-*p*-[*N*,*N*-bis(2-chloroethyl)amino]benzaldehydes which have previously shown antitumor activity



Scheme I

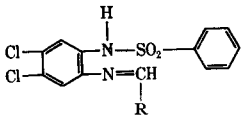
either in their own rights or in easily hydrolyzed derivatives (5–15). It was hoped that these new azomethine derivatives (II) would be even more potent antineoplastic drugs than either the active parent amine I*b* or the active aldehyde alone.

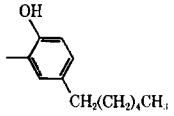
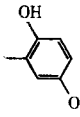
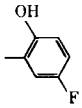
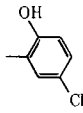
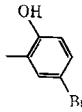
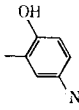
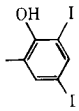
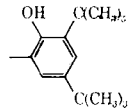
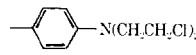
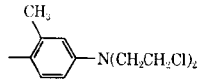
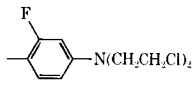


R = substituted phenyl
II

It is well known that a majority of tumors contain cells with a lower pH than cells in normal tissues. Fitch and Voegtlin (16) also have shown that the administration of glucose to tumor-bearing animals can produce an even lower pH value for the tumor cells. Since Schiff bases are one class of compounds that hydrolyze readily *in vitro* under mildly acidic conditions,

Table I—Schiff Base Derivatives of 2′-Amino-4′,5′-dichlorobenzenesulfonanilide



Compd. No.	R	Formula	Yield (pure), %	M.p.	% N Calcd.	% N Found	IR Absorptions, μ —NH- SO_2—	IR Absorptions, μ —C=N—
1		$C_{19}H_{14}Cl_2N_2O_3S$	87.0	166–168°[a]	6.64	6.50	3.14 7.50 8.57	6.20
2		$C_{25}H_{26}Cl_2N_2O_3S$	86.5	135.5–137.5°[a]	5.54	5.53	3.11 7.50 8.60	6.19
3		$C_{20}H_{16}Cl_2N_2O_4S$	92.0	189.0–190.5°[b]	6.21	5.99	3.08 7.54 8.64	6.18
4		$C_{19}H_{13}Cl_2FN_2O_3S$	89.5	179–181°[a]	6.38	6.28	3.08 7.56 8.64	6.16
5		$C_{19}H_{13}Cl_3N_2O_3S$	65.8	181–183°[a]	6.15	6.02	3.16 7.73 8.73	6.20
6		$C_{19}H_{13}BrCl_2N_2O_3S$	70.9	185–186°[a]	5.60	5.66	3.15 7.72 8.72	6.19
7		$C_{19}H_{13}Cl_2N_3O_5S$	76.5	208–210°[e] dec.	9.01	9.09	3.07 7.56 8.60	6.21
8		$C_{19}H_{12}Cl_2I_2N_2O_3S$	91.9	206–208°[d] dec.	4.16	4.46	3.28 7.66 8.63	6.19
9		$C_{27}H_{30}Cl_2N_2O_3S$	82.1	191–193°[a]	5.25	5.28	3.06 7.59 8.59	6.19
10		$C_{23}H_{21}Cl_4N_3O_2S$	89.5	192–194°[b]	7.71	7.66	3.10 7.35 8.59	6.27
11		$C_{24}H_{23}Cl_4N_3O_2S$	94.3	167–169°[b]	7.51	7.36	3.11 7.40 8.57	6.28
12		$C_{23}H_{20}Cl_2FN_3O_2S$	83.7	173–175°[c]	7.46	7.34	3.08 7.41 8.61	6.22

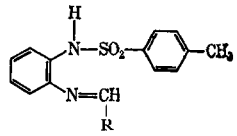
[a] Recrystallized from 2-propanol. [b] Recrystallized from 4:1 2-propanol–acetonitrile. [c] Recrystallized from 1:1 2-propanol–acetonitrile. [d] Recrystallized from 10:1 acetonitrile–*N*,*N*-dimethylformamide.

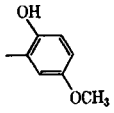
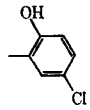
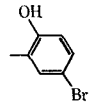
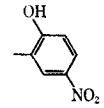
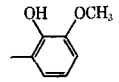
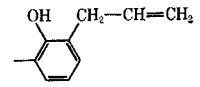
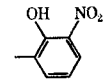
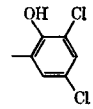
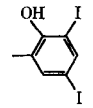
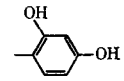
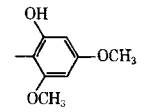
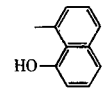
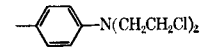
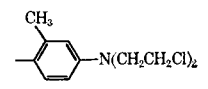
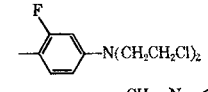
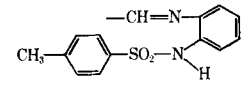
such compounds probably could be hydrolyzed selectively by the tumor cells to liberate the active aldehydes to serve as alkylating agents at the same time as the active amine is freed to act as an antimetabolite.

Even if hydrolysis of the Schiff bases does not occur at the tumor site, the compounds might still be active. Ross *et al.* (10) have pointed out that the azomethine linkage in these compounds can be regarded as an isostere of two cytotoxic agents: the azo compounds and the stilbenes.

Seventeen Schiff bases (IV) (Table II) of 2′-amino-*p*-toluenesulfonanilide (III) were also prepared (Scheme I), using the same or similar aldehydes as were used in the synthesis of Compounds II. Here, if the derivatives IV undergo hydrolysis in the mildly acidic tumor cells, the active aldehydes could still be liberated to serve as

Table II—Schiff Base Derivatives of 2′-Amino-*p*-toluenesulfonanilide



Compd. No.	R	Formula	Yield (pure), %	M.p.	%N Calcd.	%N Found	IR Absorptions, μ —NH— SO_2—	IR Absorptions, μ —C=N—
1		$C_{20}H_{18}N_2O_3S$	98.2	143–144°[a]	7.65	7.82	3.05 7.60 8.73	6.21
2		$C_{21}H_{20}N_2O_4S$	89.5	174–175°[a]	7.07	7.23	3.06 7.51 8.59	6.19
3		$C_{20}H_{17}ClN_2O_3S$	90.2	154–155°[a]	6.99	7.25	3.09 7.55 8.65	6.22
4		$C_{20}H_{17}BrN_2O_3S$	81.9	159.5–160.5°[a]	6.29	6.34	3.08 7.50 8.59	6.29
5		$C_{20}H_{17}N_3O_5S$	96.0	196–197°[b]	10.21	10.44	3.17 7.60 8.72	6.28
6		$C_{21}H_{20}N_2O_4S$	95.1	140.5–142.5°[a]	7.07	6.88	3.11 7.58 8.67	6.23
7		$C_{23}H_{22}N_2O_3S$	82.4	120.0–121.5°[a]	6.89	7.00	3.09 7.55 8.61	6.21
8		$C_{20}H_{17}N_3O_5S$	93.6	161–163°[a]	10.21	10.31	3.10 7.53 8.64	6.19
9		$C_{20}H_{15}Cl_2N_2O_3S$	85.0	171.5–173.5°[a]	6.43	6.20	3.06 7.55 8.58	6.14
10		$C_{20}H_{16}I_2N_2O_3S$	83.9	171–173°[c] dec.	4.53	4.78	3.08 7.60 8.64	6.20
11		$C_{20}H_{16}N_2O_4S$	87.6	188–189°[a] dec.	7.32	7.17	3.11 7.50 8.63	6.10 6.18
12		$C_{22}H_{22}N_2O_5S$	56.3	195–197°[b]	6.57	6.70	3.05 7.50 8.57	6.16
13		$C_{24}H_{20}N_2O_3S$	96.2	186.5–187.5°[d]	6.73	6.52	3.10 7.56 8.60	6.16
14		$C_{24}H_{25}Cl_2N_3O_2S$	94.1	125–126°[b]	8.57	8.50	3.11 7.42 8.64	6.25
15		$C_{25}H_{27}Cl_2N_3O_2S$	98.6	146–147°[b]	8.33	8.42	3.10 7.40 8.62	6.21
16		$C_{24}H_{24}Cl_2FN_3O_2S$	75.5	163–164°[b]	8.26	8.19	3.07 7.39 8.62	6.19
17		$C_{28}H_{26}N_4O_4S_2$	40.4	132–133°[e] dec.	10.25	9.96	2.93 7.40 8.55	6.24

[a] Recrystallized from 2-propanol. [b] Recrystallized from 4:1 2-propanol–acetonitrile. [c] Recrystallized from 1:1 2-propanol–acetonitrile. [d] Recrystallized from acetonitrile. [e] Washed with water, acetone, methanol, and diethyl ether but not recrystallized from any solvent.

alkylating agents but the freed amine (III) would not have any antitumor activity (17). Thus, the primary functions of III would be to serve as a carrier of the active aldehydes to the tumor site and to direct them into the cellular metabolism. III could also serve as a protector of the aldehydes and prevent their destruction through oxidation, reduction, or whatever before they reached the tumor cells where they could be freed to function as antitumor agents.

Antitumor evaluation of the compounds in Tables I and II was carried out[1] using the test system for leukemia L-1210 (intraperitoneal). No appreciable activity was shown by any of the compounds in Tables I and II with this particular test system.

EXPERIMENTAL[2]

2′-Amino-4′,5′-dichlorobenzenesulfonanilide, Ib—Seventy-five grams (0.424 mole) of 4,5-dichloro-*o*-phenylenediamine was suspended in 800 ml. of a 3:2 ethanol–water mixture and cooled to 0–5° in an ice bath. With vigorous stirring and maintenance of the temperature at 0–5°, 61.8 g. (0.350 mole) of benzenesulfonyl chloride was added dropwise over 5 hr. After complete addition, the stirring was continued for 4 hr. with the ice bath removed. Three hundred milliliters of 2.0 *N* hydrochloric acid was then added, and the mixture was stirred another hour. Suction filtration of the reaction mixture provided a wine-red solution and a purple-gray precipitate. The solid was recrystallized from 2-propanol with the hot mother liquor being decolorized with activated charcoal. White crystals of I*b* were obtained after two further recrystallizations from 2-propanol. Yield: 44.8 g., 40.4%. M.p. (lit.) 158° (2); (obs.) 163–165°. IR absorptions, μ: —$NHSO_2$—, 3.10, 7.60, and 8.64; —NH_2, 2.90, 3.00, and 6.20.

Anal.—Calcd. for $C_{12}H_{10}Cl_2N_2O_2S$: N, 8.83. Found: N, 8.80.

Recovery of 22.8 g. of 4,5-dichloro-*o*-phenylenediamine was effected by neutralization of the wine-red solution with 50% aqueous sodium hydroxide.

2′-Amino-4′,5′-dichlorobenzenesulfonanilide Schiff Base Derivatives, II (Table I)—The synthesis of this series of compounds is illustrated by the preparation of 2′-{[5-(*n*-hexyl)salicylidene]amino}-4′,5′-dichlorobenzenesulfonanilide. To a stirring solution of 2.30 g. (0.00730 mole) of 2′-amino-4′,5′-dichlorobenzenesulfonanilide in 50 ml. of absolute ethanol was added dropwise, over 15 min., 1.50 g. (0.00750 mole) of 5-(*n*-hexyl)salicylaldehyde (18) dissolved in 75 ml. of absolute ethanol. The mixture was refluxed for 15 min., chilled, and filtered. The tan solid obtained was recrystallized from 2-propanol to give fluffy, light-yellow crystals. Yield: 3.20 g., 86.5%. M.p. 135.5–137.5°.

Anal.—Calcd. for $C_{25}H_{26}Cl_2N_2O_3S$: N, 5.54. Found: N, 5.53.

2′-Amino-*p*-toluenesulfonanilide, III—A solution of 48.7 g. (0.450 mole) of *o*-phenylenediamine in 300 ml. of a 1:1 aqueous ethanol mixture was cooled to 0–5° in an ice bath. Over a span of 3 hr., 57.2 g. (0.300 mole) of *p*-toluenesulfonyl chloride was added in small portions with rapid stirring at 0–5°. The stirring at 0–5° was continued for another hour after the addition was completed; then the ice bath was removed. Two hundred fifty milliliters of 2.0 *N* hydrochloric acid was added, and stirring was continued for 60 min. at room temperature. After the disubstituted compound had been removed by suction filtration, the clear, dark-red filtrate was neutralized with 50% aqueous sodium hydroxide until a precipitate began to form. To complete the neutralization, solid sodium bicarbonate was slowly added with stirring until the evolution of carbon dioxide ceased. The mixture was chilled thoroughly in an ice bath and then filtered with suction. The resulting off-white solid was recrystallized from 2-propanol to give fluffy, white crystals of III. Yield: 63.8 g., 81.1%. M.p. (lit.) 114° (19), 135–136° (20), 142° (21); (obs.) 139–140°. IR absorptions, μ: —$NHSO_2$—, 3.16, 7.60, and 8.78; —NH_2, 2.91, 3.00, and 6.19.

Anal.—Calcd. for $C_{13}H_{14}N_2O_2S$: N, 10.68. Found: N, 10.65.

2′-Amino-*p*-toluenesulfonanilide Schiff Base Derivatives, IV (Table II)—The following synthesis for 2′-{[2-fluoro-4-(*N*,*N*-bis(2-chloroethyl)amino)benzylidene]amino}-*p*-toluenesulfonanilide is typical of the procedure used for preparing this series of compounds. Five and twenty-five hundredths grams (0.0200 mole) of 2′-amino-*p*-toluenesulfonanilide was dissolved in 50 ml. of dry methanol. To this was added dropwise, with stirring, a second solution of 5.03 g. (0.0220 mole) of 2-fluoro-4-[*N*,*N*-bis(2-chloroethyl)amino]-benzaldehyde (13) contained in 75 ml. of hot methanol. The addition took 15 min. and was followed by 30 min. of refluxing. The reaction mixture was cooled in an ice bath and filtered to obtain a dirty yellow solid. Recrystallization of this solid from a 4:1 2-propanol–acetonitrile mixture afforded bright-yellow crystals which were moderately light sensitive. Yield: 7.70 g., 75.5%. M.p. 163–164°.

Anal.—Calcd. for $C_{24}H_{24}Cl_2FN_3O_2S$: N, 8.26. Found: N, 8.19.

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[2] All melting points were taken in open capillaries on a Thomas-Hoover melting point apparatus and are uncorrected. The elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. The IR spectra were determined in KBr disks on a Perkin-Elmer Infracord spectrophotometer. Aldehydes and other starting materials used were either reagent grade or were purified by distillation or recrystallization from appropriate solvents.